ZOLADEX® (goserelin implant) 3.6 mg

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZOLADEX safely and effectively.

See full prescribing information for ZOLADEX.

ZOLADEX® (goserelin implant) 3.6 mg
Initial U.S. Approval: 1989

INDICATIONS AND USAGE

ZOLADEX is a Gonadotropin Releasing Hormone (GnRH) agonist indicated for:

- Use in combination with flutamide for the management of locally confined carcinoma of the prostate (1.1)
- Palliative treatment of advanced carcinoma of the prostate (1.2)
- The management of endometriosis (1.3)
- Use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding (1.4)
- Use in the palliative treatment of advanced breast cancer in pre- and perimenopausal women (1.5)

DOSAGE AND ADMINISTRATION

- ZOLADEX 3.6 mg should be administered subcutaneously every 28 days (2.1, 2.7)
- For the management of endometriosis, the recommended duration of administration is 6 months for women 18 years of age and older (2.3)

DOSE FORMS AND STRENGTHS

Implant 3.6 mg (3)

CONTRAINDICATIONS

- Hypersensitivity (4.1)
- Pregnancy unless used for treatment of advanced breast cancer (4.2)

WARNINGS AND PRECAUTIONS

- Women of Childbearing Potential and Pregnancy: Pregnancy must be excluded for use in benign gynecological conditions. Women should avoid pregnancy (5.1)
- Tumor Flare Phenomenon: Transient worsening of tumor symptoms may occur during the first few weeks of treatment with ZOLADEX, which may include ureteral obstruction and spinal cord compression. Monitor patients at risk for complications of tumor flare (5.2, 5.2)
- Hyperglycemia and Diabetes: Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH analogs. Monitor blood glucose level and manage according to current clinical practice (5.3)

ADVERSE REACTIONS

The most common, clinically significant adverse reactions occurring in >10% of men: hot flashes, sexual dysfunction, decreased erections and lower urinary tract symptoms (6)

The adverse event profile was similar for women treated for breast cancer, dysfunctional uterine bleeding or endometriosis and included (>20%): hot flushes, headache, sweating, acne, emotional lability, depression, decreased libido, vaginitis, breast atrophy, seborrhea, and peripheral edema (6)

Tumor flare can occur on the initiation of ZOLADEX for both men and women being treated for cancer (6)

To report SUSPECTED ADVERSE REACTIONS, contact TerSera Therapeutics at 1-844-334-4035 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- None

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Discontinue drug or nursing taking into account the importance of drug to the mother (8.3)
- No information available for use in Pediatric patients (8.4)
- Geriatric (8.5)
- Renal and Hepatic Impairment: No dose adjustment is necessary (8.6, 8.7)

CARDIOVASCULAR DISEASES: Increased risk of myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH analogs in men. Monitor for cardiovascular disease and manage according to current clinical practice (5.4)

Hypercalcemia: Hypercalcemia has been reported in patients with bone metastases treated with ZOLADEX. Monitor and manage appropriately (5.5)

Hypersensitivity: Systemic hypersensitivity has been reported in patients receiving goserelin/ZOLADEX implants (4.1, 5.6)

Cervical Resistance: Increase in cervical resistance may occur. Caution is recommended when dilating the cervix for endometrial ablation (5.7)

Effect on QT/QTc Interval: Androgen deprivation therapy may prolong the QT interval. Consider risks and benefits (5.8)

Injection Site Injury: Injection site injury and vascular injury have been reported during administration of ZOLADEX (5.9)

OVERDOSAGE

No information available for use in Pediatric patients (8.4)

NONCLINICAL TOXICOLOGY

- Cardiac Insufficiency
- Renal Insufficiency
- Heparin Insufficiency

CLINICAL PHARMACOLOGY

- Mechanism of Action
- Pharmacodynamics
- Pharmacokinetics

NONCLINICAL TOXICOLOGY

- Carcinogenesis, Mutagenesis, Impairment of Fertility

CLINICAL STUDIES

- Stage B2-C Prostatic Carcinoma
- Prostatic Carcinoma
- Endometriosis
- Endometrial Thinning
- Breast Cancer

HOW SUPPLIED/STORAGE AND HANDLING

PATIENT COUNSELING INFORMATION

[Continued...]

* Sections or subsections omitted from the full prescribing information are not listed.
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Stage B2-C Prostatic Carcinoma

ZOLADEX is indicated for use in combination with flutamide for the management of locally confined Stage T2b-T4a (Stage 2-C) carcinoma of the prostate. Treatment with ZOLADEX and flutamide should start 8 weeks prior to initiating radiation therapy and continue during radiation therapy [see Dosage and Administration (2.1) and Clinical Studies (14.1)].

1.2 Prostatic Carcinoma

ZOLADEX is indicated in the palliative treatment of advanced carcinoma of the prostate [see Dosage and Administration (2.2) and Clinical Studies (14.2)].

1.3 Endometriosis

ZOLADEX is indicated for the management of endometriosis, including pain relief and reduction of endometriotic lesions for the duration of therapy. Experience with ZOLADEX for the management of endometriosis has been limited to women 18 years of age and older treated for 6 months [see Dosage and Administration (2.3) and Clinical Studies (14.3)].

1.4 Endometrial Thinning

ZOLADEX is indicated for use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding [see Dosage and Administration (2.4) and Clinical Studies (14.4)].

1.5 Advanced Breast Cancer

ZOLADEX is indicated for use in the palliative treatment of advanced breast cancer in pre- and perimenopausal women.

NOTE: Caution should be taken while injecting ZOLADEX into the anterior abdominal wall due to the proximity of underlying inferior epigastric artery and its branches. To do so may displace the ZOLADEX implant.

NOTE: The needle does not retract.

7. Withdraw the needle and allow protective sleeve to slide and cover needle. Dispose of the syringe in an approved sharps collector.

NOTE: In the unlikely event of the need to surgically remove ZOLADEX, it may be localized by ultrasound.

2 DOSAGE AND ADMINISTRATION

2.1 Stage B2-C Prostatic Carcinoma

When ZOLADEX is given in combination with radiotherapy and flutamide for patients with Stage T2b-T4a (Stage B2-C) prostatic carcinoma, treatment should be started 8 weeks prior to initiating radiotherapy and should continue during radiation therapy. A treatment regimen using a ZOLADEX 3.6 mg depot 8 weeks before radiotherapy, followed in 28 days by the ZOLADEX 10.8 mg depot, can be administered. Alternatively, four injections of 3.6 mg depot can be administered at 28-day intervals, two depot preceding and two during radiotherapy.

2.2 Prostatic Carcinoma

For the management of advanced prostate cancer, ZOLADEX is intended for long-term administration unless clinically inappropriate.

2.3 Endometriosis

For the management of endometriosis, the recommended duration of administration is 6 months. Currently, there are no clinical data on the effect of treatment of benign gynecological conditions with ZOLADEX for periods in excess of 6 months.

Retreatment cannot be recommended for the management of endometriosis since safety data for retreatment are not available. If the symptoms of endometriosis recur after a course of therapy, and further treatment with ZOLADEX is contemplated, consideration should be given to monitoring bone mineral density. Clinical studies suggest the addition of Hormone Replacement Therapy (estrogens and/or progestins) to ZOLADEX is effective in reducing the bone mineral loss which occurs with ZOLADEX alone without compromising the efficacy of ZOLADEX in relieving the symptoms of endometriosis. The addition of Hormone Replacement Therapy may also reduce the occurrence of vasomotor symptoms and vaginal dryness associated with hysterectomy. The optimal drugs, dose and duration of treatment has not been established.

2.4 Endometrial Thinning

For use as an endometrial-thinning agent prior to endometrial ablation, the dosing recommendation is one or two depot (with each depot given four weeks apart). When one depot is administered, surgery should be performed at four weeks. When two dosps are administered, surgery should be performed within two to four weeks following administration of the second depot.

2.5 Breast Cancer

For the management of advanced breast cancer, ZOLADEX is intended for long-term administration unless clinically inappropriate.

2.6 Renal or Hepatic Impairment

No dosage adjustment is necessary for patients with renal or hepatic impairment.

2.7 Administration Technique

The proper method of administration of ZOLADEX is described in the instructions that follow.

1. Put the patient in a comfortable position with the upper part of the body slightly raised. Prepare an area of the anterior abdominal wall below the navel line with an alcoholic swab. NOTE: Caution should be taken while injecting ZOLADEX into the anterior abdominal wall due to the proximity of underlying inferior epigastric artery and its branches.

2. Examine the foil pouch and syringe for damage. Remove the syringe from the opened foil protective sleeve will automatically begin to slide to cover the needle.

3. Grasp the red plastic safety tab and pull away from the syringe, and discard. Remove needle cover. Unlike liquid injections, there is no need to remove air bubbles as attempts to do so may displace the ZOLADEX implant.

4. Holding the syringe around the protective sleeve, using an aseptic technique, pinch the skin of the patient’s anterior abdominal wall below the navel line. With the bevel of the needle facing up, insert the needle at a 30 to 45 degree angle to the skin in one continuous deliberate motion until the protective sleeve touches the patient’s skin.

NOTE: The ZOLADEX syringe cannot be used for aspiration. If the hypodermic needle penetrates a large vessel, blood will be seen instantly in the syringe chamber. If a vessel is penetrated, withdraw the needle and inject with a new syringe elsewhere. Monitor patients for signs or symptoms of abdominal hemorrhage. Use extra care when administering ZOLADEX to patients with a low BMI and to patients receiving full dose anticoagulation [see Warnings and Precautions (5.9)].

5. Do not penetrate into muscle or peritoneum.

6. To administer the ZOLADEX implant and to activate the protective sleeve, grasp the barrel at the finger grip and depress the plunger until you cannot depress it any further. If the plunger is not depressed fully, the protective sleeve will NOT activate. When the protective sleeve ‘clicks’, the protective sleeve will automatically begin to slide to cover the needle.

NOTE: The needle does not retract.

7. Withdraw the needle and allow protective sleeve to slide and cover needle. Dispose of the syringe in an approved sharps collector.

NOTE: In the unlikely event of the need to surgically remove ZOLADEX, it may be localized by ultrasound.

3 DOSAGE FORMS AND STRENGTHS

ZOLADEX is supplied as a sterile and totally biodegradable 2.5–lactic acid and glycolic acid copolymer vehicle containing 3.6 mg or 7.2 mg acetate or 3.6 mg or 7.2 mg acetate equivalent to 3.6 mg or 7.2 mg of goserelin, in a disposable syringe device fitted with a 16-gauge × 36 +/- 0.5 mm siliconized hypodermic needle with protective needle sleeve [SafeSystem® Syringe] (NDC 70720-950-36).

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Anaphylactic reactions to ZOLADEX have been reported in the medical literature. ZOLADEX is contraindicated in those patients who have a known hypersensitivity to GnRH, GnRH agonist analogues or any of the components in ZOLADEX [see Warnings and Precautions (5.6)].

4.2 Pregnancy

ZOLADEX is contraindicated during pregnancy unless ZOLADEX is being used for palliative treatment of advanced breast cancer. ZOLADEX can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, the patient should be apprised of the potential hazard to the fetus. There is an increased risk for pregnancy loss due to expected hormone changes that occur with ZOLADEX treatment [see Use in Specific Populations (8.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Women of Childbearing Potential and Pregnancy

Before starting treatment with ZOLADEX, pregnancy must be excluded for women using ZOLADEX for benign gynecological conditions. Women of childbearing potential should be advised to avoid becoming pregnant. Effective nonhormonal contraception must be used by all premenopausal women during ZOLADEX therapy and for 12 weeks following discontinuation of therapy. When used every 28 days, ZOLADEX usually inhibits ovulation and stops menstruation; however, pregnancy prevention is not ensured. Effects on reproductive function are expected to occur with chronic administration as a result of the anti-gonadotrophic properties of the drug. Based on mechanism of action in humans and findings of increased pregnancy loss in animal studies, ZOLADEX can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, the patient should be apprised of the potential hazard to the fetus [see Use in Specific Populations (8.1)].

5.2 Tumor Flare Phenomenon

Initially, ZOLADEX, like other GnRH agonists, causes transient increases in serum levels of testosterone in men with prostate cancer, and estrogen in women with breast cancer. Transient worsening of symptoms, or the occurrence of additional signs and symptoms of prostate or breast cancer, may occasionally develop during the first few weeks of ZOLADEX treatment. A small number of patients may experience a temporary increase in bone pain, which can be managed symptomatically.

As with other GnRH agonists, isolated cases of ureteral obstruction and spinal cord compression have been observed in patients with prostate cancer. If spinal cord compression or renal impairment secondary to ureteral obstruction develops, standard treatment of these complications should be instituted. For extreme cases in prostate cancer patients, an immediate orthoichotomy should be considered.

5.3 Hyperglycemia and Diabetes

Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycemia may represent development of diabetes mellitus or worsening of glycemic control in patients with diabetes. Monitor blood glucose and/or glycosylated hemoglobin (HbA1c) periodically in patients receiving a GnRH agonist and manage with current practice for treatment of hyperglycemia or diabetes [see Patient Counseling Information (17.1)].

5.4 Cardiovascular Diseases

Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH agonists in men. The risk appears low based on the reported odds ratios, and should be evaluated carefully along with cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving a GnRH agonist should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice [see Patient Counseling Information (17.1)].

5.5 Hypercalcemia

As with other GnRH agonists or hormonal therapies (antiestrogens, estrogens, etc.), hypercalcemia has been reported in some prostate and breast cancer patients with bone metastases after starting treatment with ZOLADEX. If hypercalcemia occurs, appropriate treatment measures should be initiated.
In the controlled clinical trials of ZOLADEX versus orchiectomy, the following events were reported:

- Complications related to surgery were reported in 18% of the orchiectomy patients, while only 3% of ZOLADEX patients reported adverse reactions at the injection site. The surgical complications included wound seepage (3.1%), scrotal hematoma (2.8%), incisional discomfort (1.6%) and skin necrosis (1.2%).

### Table 1 ADVERSE EVENTS DURING ACUTE RADIATION THERAPY (within 90 days of radiation therapy)

<table>
<thead>
<tr>
<th></th>
<th>ZOLADEX (n=231)</th>
<th>ORCHIECTOMY (n=254)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event</td>
<td>% All</td>
<td>% All</td>
</tr>
<tr>
<td>Rectum/Large Bowel</td>
<td>80</td>
<td>76</td>
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<tr>
<td>Bladder</td>
<td>58</td>
<td>60</td>
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<tr>
<td>Skin</td>
<td>37</td>
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### Table 2 ADVERSE EVENTS DURING LATE RADIATION PHASE (after 90 days of radiation therapy)

<table>
<thead>
<tr>
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<th>ZOLADEX (n=231)</th>
<th>ORCHIECTOMY (n=254)</th>
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</thead>
<tbody>
<tr>
<td>Adverse Event</td>
<td>% All</td>
<td>% All</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36</td>
<td>40</td>
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<tr>
<td>Cystitis</td>
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<td>16</td>
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<tr>
<td>Rectal Bleeding</td>
<td>14</td>
<td>20</td>
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<tr>
<td>Proctitis</td>
<td>8</td>
<td>8</td>
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<tr>
<td>Hematuria</td>
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### Table 3 TREATMENT RECEIVED

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<th>ZOLADEX (n=242)</th>
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<tr>
<td>Adverse Event</td>
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<td>%</td>
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<tr>
<td>Hot Flashes</td>
<td>62</td>
<td>53</td>
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<tr>
<td>Sexual Dysfunction</td>
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<td>15</td>
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<tr>
<td>Decreased Erections</td>
<td>18</td>
<td>16</td>
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<tr>
<td>Lower Urinary Tract Symptoms</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Lethargy</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Pain (worsened in the first 30 days)</td>
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<td>3</td>
</tr>
<tr>
<td>Edema</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Upper Respiratory Infection</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Rash</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Sweating</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Anorexia</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
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<td>3</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5</td>
<td>1</td>
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<tr>
<td>Nausea</td>
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<td>2</td>
</tr>
<tr>
<td>Complications of Surgery</td>
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### Table 4 TREATMENT RECEIVED

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<tr>
<td>Adverse Event</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Hot Flashes</td>
<td>96</td>
<td>67</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>75</td>
<td>43</td>
</tr>
<tr>
<td>Headache</td>
<td>75</td>
<td>63</td>
</tr>
<tr>
<td>Emotional Lability</td>
<td>60</td>
<td>56</td>
</tr>
<tr>
<td>Libido Decreased</td>
<td>61</td>
<td>44</td>
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<tr>
<td>Sweating</td>
<td>54</td>
<td>30</td>
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<tr>
<td>Depression</td>
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<td>Acne</td>
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<tr>
<td>Breast Atrophy</td>
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<td>52</td>
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<tr>
<td>Seborrhea</td>
<td>26</td>
<td>34</td>
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<tr>
<td>Breast Enlargement</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Pelvic Symptoms</td>
<td>18</td>
<td>23</td>
</tr>
<tr>
<td>Pain</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Libido Increased</td>
<td>12</td>
<td>19</td>
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<tr>
<td>Infection</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Anemia</td>
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<td>13</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>14</td>
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<tr>
<td>Hirsutism</td>
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<td>Insomnia</td>
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<td>Breast Pain</td>
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<td>Abdominal Pain</td>
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<tr>
<td>Back Pain</td>
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<td>13</td>
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<td>H. P. Syndrome</td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Application Site Reaction</td>
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</tr>
<tr>
<td>Voice Alterations</td>
<td>3</td>
<td>8</td>
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<tr>
<td>Pharyngitis</td>
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<tr>
<td>Hair Disorders</td>
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<td>Myalgia</td>
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<tr>
<td>Nervousness</td>
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<tr>
<td>Weight Gain</td>
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<td>Leg Cramps</td>
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<td>Increased Appetite</td>
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<td>Pruritus</td>
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<td>6</td>
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<tr>
<td>Hypertonia</td>
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</tbody>
</table>

Additional adverse event data was collected for the combination therapy with radiation group over both the hormonal treatment and hormonal treatment plus radiation phases of the study. Adverse experiences occurring in more than 5% of patients in this group, over both parts of the study, were hot flashes (46%), diarrhea (40%), nausea (9%), and skin rash (8%).

### 6.2 Prostatic Carcinoma

ZOLADEX has been found to be generally well tolerated in clinical trials. Adverse reactions reported in these trials were rarely severe enough to result in the patients’ withdrawal from ZOLADEX treatment. As seen with other hormonal therapies, the most commonly observed adverse events during ZOLADEX therapy were due to the expected physiological effects.
The following adverse events not already listed above were reported at a frequency of 1% or greater, regardless of causality. In ZOLADEX-treated women from all clinical trials: WHOLE BODY – edema; MUSCULOSKELETAL – arthralgia, joint disorder; CNS – anxiety, somnolence, thinking abnormal; RESPIRATORY – bronchitis, cough increased, rhinitis, sinusitis; SKIN – alopecia, dry skin, rash, skin discoloration; SPECIAL SENSES – amblyopia, dry eyes; UROGENITAL – dysmenorrhea, urinary frequency, urinary tract infection, vaginal hemorrhage.

6.5 Endometrial Thinning

The following adverse events were reported at a frequency of 5% or greater in premenopausal women presenting with dysfunctional uterine bleeding in Trial 0022 for endometrial thinning. These results indicate that headache, hot flushes and sweating were more common in the ZOLADEX group than in the placebo group.

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>ZOLADEX (n=57)</th>
<th>Placebo (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>22%</td>
<td>22%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>Pelvic Pain</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>4%</td>
<td>7%</td>
</tr>
</tbody>
</table>

6.6 Breast Cancer

The adverse event profile for women with advanced breast cancer treated with ZOLADEX is consistent with the profile described above for women treated with ZOLADEX for endometriosis. In a controlled clinical trial (SWOG-8692) comparing ZOLADEX with oophorectomy in premenopausal and perimenopausal women with advanced breast cancer, the following events were reported at a frequency of 5% or greater in either treatment group regardless of causality.

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>ZOLADEX (n=57)</th>
<th>Placebo (n=55)</th>
</tr>
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<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>4%</td>
<td>7%</td>
</tr>
</tbody>
</table>

6.7 Hormone Replacement Therapy

Clinical studies suggest the addition of Hormone Replacement Therapy (estrogens and/or progestins) to ZOLADEX may decrease the occurrence of vasomotor symptoms and vaginal dryness associated with hypoestrogenism without compromising the efficacy of ZOLADEX in relieving pelvic symptoms. The optimal drugs, dose and duration of treatment has not been established.

6.8 Changes in Bone Mineral Density

After 6 months of ZOLADEX treatment, 109 female patients treated with ZOLADEX showed an average 2.4% BMD loss compared to pretreatment values. Twenty-eight of the 109 patients were assessed for BMD at 12 months posttherapy. Data from these patients showed an average decrease of 2.5% in BMD compared to pretreatment values. These data suggest a possibility of partial reversibility. Clinical studies suggest the addition of Hormone Replacement Therapy (estrogens and/or progestins) to ZOLADEX is effective in reversing the bone mineral loss which occurs with ZOLADEX alone without compromising the efficacy of ZOLADEX in relieving the symptoms of endometriosis. The optimal drugs, dose and duration of treatment has not been established [see Patient Counseling Information (17.2)].

6.9 Changes in Laboratory Values During Treatment

Plasma Enzymes: Elevation of liver enzymes (AST, ALT) have been reported in female patients exposed to ZOLADEX (representing less than 1% of all patients).

Lipids: In a controlled trial, ZOLADEX therapy resulted in a minor, but statistically significant effect on reducing the bone mineral loss which occurs with ZOLADEX alone without compromising the efficacy of ZOLADEX in relieving the symptoms of endometriosis. The optimal drugs, dose and duration of treatment has not been established [see Patient Counseling Information (17.2)].

6.10 Postmarketing Experience

The following adverse reactions have been identified following post-approval use of ZOLADEX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Bone Mineral Density: Osteoporosis, decreased bone mineral density and bone fracture in men [see Patient Counseling Information (17.1) and (17.2)].

Cardiovascular: Deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke, and transient ischemic attack have been observed in women treated with GnRH agonists. Although a temporal relationship was reported in some cases, most cases were confounded by risk factors or concomitant medication use. It is not known if there is a causal association between the use of GnRH analogs and these events.

Ovarian Gyn: Ovarian cyst formation and, in combination with gonadotropins, ovarian hyperstimulation syndrome (OHSS).

Changes in Blood Pressure: Hypotension and hypertension have been reported. These changes are usually transient, resolving either during continued therapy or after cessation of therapy.

Pituitary Apoplexy and Tumors: Pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) and pituitary adenoma have been diagnosed. Most of the pituitary apoplexy cases occurred within 2 weeks of the first dose, and some occurred within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required. Pituitary tumors have been reported.

Acne: Usually within one month of starting treatment.

Other Adverse Reactions: Psychotic disorders, convulsions and mood swings.

7 DRUG INTERACTIONS

No formal drug-drug interaction studies have been performed. No confirmed interactions have been reported between ZOLADEX and other drugs.

7.1 Drug/Laboratory Test Interactions

Administration of ZOLADEX in therapeutic doses results in suppression of the pituitary-gonadal system. Because of this suppression, diagnostic tests of pituitary-gonadotropic and gonadal functions conducted during treatment and until the resumption of menses may show results which are misleading. Normal function is usually restored within 12 weeks after treatment is discontinued.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

ZOLADEX is contraindicated during pregnancy unless ZOLADEX is being used for palliative treatment of advanced breast cancer. There are no adequate and well-controlled studies in pregnant women using ZOLADEX. Based on mechanism of action in humans and findings of increased pregnancy loss in animal studies, ZOLADEX can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, the patient should be apprised of the potential hazard to the fetus. There is an increased risk for pregnancy loss due to expected hormone changes that occur with ZOLADEX treatment.

ZOLADEX crosses the placenta in rats and rabbits following subcutaneous administration. Administration of goserelin to pregnant rats and rabbits during organogenesis resulted in increased preimplantation loss and increased resorptions. When pregnant rats received goserelin throughout gestation and lactation, there was a dose-related increase in umbilical hernia in offspring. Additional reproduction studies in rats, goserelin decreased fetus and pup survival. Human dose/exposure multiples could not be calculated from available animal data. Actual animal doses: rat (≥ 2 mcg/kg/day for pregnancy loss; > 10 mcg/kg/day for umbilical hernia in offspring); rabbits (> 20 mcg/kg/day).

8.3 Nursing Mothers

It is not known if goserelin is excreted in human milk. Goserelin is excreted in the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in breastfed infants, ZOLADEX, a decision should be made to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.
The absorption of radiolabeled drug was rapid, and the peak blood radioactivity levels occurred following the last implant administration in all but rare cases. There is no pharmacokinetic data with goserelin in patients with severe hepatic insufficiency.

10 OVERDOSAGE

Animal studies indicate that no increased pharmacologic effect occurred at higher doses or more frequent administration. Subcutaneous doses of the drug as high as 1 mg/kg/day in rats and dogs did not produce any nonendocrine related sequelae; this dose is up to 250 times the estimated human daily dose based on the body surface area. If overdosage occurs, it should be managed symptomatically.

11 DESCRIPTION

ZOLADEX (goserelin implant) is a GnRH agonist. Goserelin acetate is chemically described as an acetate salt of (D- Ser(Bu)6, Arg8, Leu9, Pro10, Azgly11)-Leu-Arg-Pro-Azgly-NH2, where (D-Ser(Bu)6) is tert-butyloxycarbonyl-D-serine, Arg is arginine, Leu is leucine, Pro is proline, and Azgly is azaglycine. Goserelin is a synthetic decapeptide analogue of GnRH. Goserelin acts as an inhibitor of pituitary gonadotropin secretion when administered in the biodegradable formulation. ZOLADEX is a synthetic decapeptide analogue of GnRH. Goserelin acetate is chemically described as an acetate salt of (D-Ser(Bu)6, Arg8, Leu9, Pro10, Azgly11)-Leu-Arg-Pro-Azgly-NH2, where (D-Ser(Bu)6) is tert-butyloxycarbonyl-D-serine, Arg is arginine, Leu is leucine, Pro is proline, and Azgly is azaglycine. Goserelin is a synthetic decapeptide analogue of GnRH. Goserelin acts as an inhibitor of pituitary gonadotropin secretion when administered in the biodegradable formulation.

Goserelin is released from the depot at a much slower rate initially for the first 8 days, and then there is more rapid and continuous release for the remainder of the 28-day dosing period. Despite the change in the releasing rate of goserelin, administration of ZOLADEX every 28 days resulted in testosterone levels that were suppressed to and maintained in the range normally observed in surgically castrated men.

When ZOLADEX 3.6 mg depot was used for treating male and female patients with normal renal and hepatic function, there was no significant evidence of drug accumulation. However, in clinical trials the minimum serum levels of a few patients were increased. These levels can be attributed to interpatient variation.

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Distribution

The apparent volumes of distribution determined after subcutaneous administration of 250 mcg aqueous solution of goserelin were 44.1 and 20.3 liters for males and females, respectively. The plasma protein binding of goserelin obtained from one sample was found to be 27.3%.

Metabolism

Metabolism of goserelin, by hydrolysis of the C-terminal amino acids, is the major clearance mechanism. The major circulating component in serum appeared to be 1-7 fragment, and the major component presented in serum in patients with healthy male patients was 5-10 fragment. The metabolism of goserelin in humans yields a similar but narrow profile of metabolites to that found in other species. All metabolites found in humans have also been found in toxicology species.

Excretion

Clearance of goserelin following subcutaneous administration of the solution formulation of goserelin is very rapid and occurs via a combination of hepatic metabolism and urinary excretion. Metabolites of subcutaneous goserelin labeled solution formulation dose of goserelin is excreted in urine. Approximately 20% of the dose in urine is accounted for by unchanged goserelin. The total body clearance of goserelin (administered subcutaneously as a 3.6 mg depot) was significantly (p<0.05) greater (163.9 versus 110.5 L/min) in females compared to males.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Subcutaneous implantation of goserelin in male and female rats once for 4 weeks for 1 study and recovery for 2 weeks at doses of about 80 and 150 mcg/kg (males) and 50 and 100 mcg/kg (females) daily resulted in an increased incidence of pituitary adenomas. An increased incidence of pituitary adenomas was also observed following subcutaneous implant of goserelin in rats at similar dose levels for a period of 72 weeks in males and 101 weeks in females. The relevance of the rat pituitary adenomas to humans has not been established. Subcutaneous implants of goserelin every 3 weeks for 2 years delivered to mice at doses of up to 2400 mcg/kg/day resulted in an increased incidence of histiocytic sarcoma of the vertebal column and femur. Human dose/exposure multiples could not be calculated from available animal data.

Mutagenicity tests using bacterial and mammalian systems for point mutations and cytogenetic markers have not shown a specific genotoxic potential of goserelin.

Administration of goserelin led to changes that were consistent with gonadal suppression in both male and female rats as a result of its endocrine action. In male rats administered 500-1000 mcg/kg/day, a decrease in weight and atrophic histological changes were observed in the testes, epididymis, seminal vesicle and prostate gland with complete suppression of spermatogenesis. In female rats, administration of 25-1500 mcg/kg/day, suppression of ovarian function led to decreased size and weight of ovaries and secondary sex organs; follicular development was arrested at the antral stage and the corpora lutea were reduced in size and number. Except for the tests, almost complete histologic reversal of these effects in males and females was observed several weeks after dosing was stopped; however, fertility and general reproductive function were reduced in those that became pregnant after goserelin was discontinued. Fertile matings occurred within 2 weeks after cessation of dosing, even though total recovery of reproductive function may not have occurred before mating took place; and, the ovulation rate, the corresponding implantation rate, and number of live fetuses were reduced. Based on histological examination, drug effects on reproductive organs were reversible in male rats. Administration of 107-214 mcg/kg/day goserelin when drug treatment was stopped after continuous administration for 1 year. Human dose/exposure multiples could not be calculated from available animal data.

14 CLINICAL STUDIES

14.1 Stage B2-C Prostatic Carcinoma

The effects of hormonal treatment combined with radiation were studied in 466 patients (251 ZOLADEX + flutamide + radiotherapy, 255 radiotherapy alone) with bulky primary tumors confined to the prostate (stage B2) or extending beyond the capsule (stage C), with or without pelvic node involvement. In this multicentered, controlled trial, administration of ZOLADEX (3.6 mg depot) and flutamide capsules (250 mg t.i.d.) prior to and during radiation was associated with a significantly lower rate of local failure compared to radiation alone (16% vs 33% at 4 years; P<0.001). The combination therapy also resulted in a trend toward reduction in the incidence of distant metastases (27% vs 36% at 4 years, P=0.058). Median disease-free survival was significantly increased in patients who received complete hormonal therapy combined with radiation as compared to those patients who received radiation alone (4.4 vs 2.6 years, P=0.001). Inclusion of normal PSA level as a criterion for disease-free survival also resulted in significantly increased median disease-free survival in patients receiving the combination therapy (2.7 vs 1.5 years, P<0.001).
14.2 Prostate Carcinoma
In controlled studies of patients with advanced prostatic cancer comparing ZOLADEX to orchectomy, the long-term endocrine responses and objective responses were similar between the two treatment arms. Additionally, duration of survival was similar between the two treatment arms in a comparative trial.

14.3 Endometriosis
In controlled clinical studies using the 3.6 mg formulation every 28 days for 6 months, ZOLADEX was shown to be as effective as danazol therapy in relieving clinical symptoms (dysmenorrhea, dyspareunia and pelvic pain) and signs (pelvic tenderness, pelvic induration) of endometriosis. Reduction in the size of endometrial lesions as determined by laparoscopy and ultrasound was also seen with ZOLADEX. In one study comparing ZOLADEX with danazol (800 mg/day), 63% of ZOLADEX-treated patients and 42% of danazol-treated patients had a greater than or equal to 50% reduction in the extent of endometrial lesions. In the second study comparing ZOLADEX with danazol (600 mg/day), 63% of ZOLADEX-treated and 51% of danazol-treated patients had a greater than or equal to 50% reduction in the extent of endometrial lesions. The clinical significance of a decrease in endometriotic lesions is not known at this time; and in addition, laparoscopic staging of endometriosis does not necessarily correlate with severity of symptoms.

In these two studies, ZOLADEX led to amenorrhea in 92% and 80%, respectively, of all treated women within 8 weeks after initial administration. Menses usually resumed within 8 weeks following completion of therapy. Within 4 weeks following initial administration, clinical symptoms were significantly reduced, and at the end of treatment were, on average, reduced by approximately 84%.

During the first two months of ZOLADEX use, some women experience vaginal bleeding of variable duration and intensity. In all likelihood, this bleeding represents estrogen withdrawal bleeding, and is expected to stop spontaneously.

There is insufficient data to determine whether pregnancy rates are enhanced or adversely affected by the use of ZOLADEX.

14.4 Endometrial Thinning
Two trials were conducted with ZOLADEX prior to endometrial ablation for dysfunctional uterine bleeding.

Trial 0022, was a double-blind, prospective, randomized, parallel-group multicenter trial conducted in 358 premenopausal women with dysfunctional uterine bleeding. Eligible patients were randomized to receive either two depot of ZOLADEX 3.6 mg (n=180) or two placebo injections (n=178). Administration of the first depot of ZOLADEX was given at the time of hysterectomy or the first depot of placebo was given at the time of hysterectomy or oophorectomy. Objective tumor responses were seen regardless of ER status, as shown in the following table.

Table 8  OBJECTIVE RESPONSE BY ER STATUS

<table>
<thead>
<tr>
<th>Phase II (N=228)</th>
<th>Trial 2302 (N=159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>43/119 (36)</td>
</tr>
<tr>
<td>Negative</td>
<td>6/33 (18)</td>
</tr>
<tr>
<td>Unknown</td>
<td>20/76 (26)</td>
</tr>
</tbody>
</table>

16. HOW SUPPLIED/STORAGE AND HANDLING
ZOLADEX is supplied as a sterile and totally biodegradable L-D,lactic and glycolic acid copolymer impregnated with 3.6 mg goserelin acetate, equivalent to 3.6 mg of goserelin, in a disposable device fitted with a 16-gauge x 36 +/- 0.5 mm siliconized hypodermic needle with protective needle sleeve [SafeSystem® Syringe] (NDC 70720-950-36). The unit is sterile and comes in a sealed, light- and moisture-proof, aluminum foil laminate pouch containing a desiccant capsule. Store at room temperature (do not exceed 25°C [77°F]).

17. PATIENT COUNSELING INFORMATION
17.1 Males
The use of ZOLADEX in patients at particular risk of developing urethral obstruction or spinal cord compression should be considered carefully and the patients monitored closely during the first month of therapy. Patients with urethral obstruction or spinal cord compression should have appropriate treatment initiated before initiation of ZOLADEX therapy [see Warnings and Precautions (5.2) and Adverse Reactions (6.2)].

The use of GnRH agonists may cause a reduction in bone mineral density. In men, data suggest the use of a bisphosphonate in combination with a GnRH agonist may reduce bone mineral loss [see Adverse Reactions (6.8) and (6.10)].

17.2 Females
1. Menstruation should stop with effective doses of ZOLADEX. The patient should notify her physician if regular menstruation persists. Patients missing one or more successive doses of ZOLADEX may experience breakthrough menstrual bleeding [see Warnings and Precautions (5.1)].

2. ZOLADEX should not be used in a pregnant or breastfeeding woman except for the palliative treatment of advanced breast cancer. ZOLADEX may harm the fetus and increase the risk for pregnancy loss [see Contraindications (4.2), Warnings and Precautions (5.1) and Use in Specific Populations (8.1)].

3. A woman should not begin ZOLADEX treatment if she has undiagnosed abnormal vaginal bleeding. Patients should be informed that bleeding or spotting, including the use of tampons, which may be confused with premenstrual bleeding, may occur prior to the onset of amenorrhea [see Clinical Studies (14.3)].

4. Premenopausal women using ZOLADEX must use nonhormonal contraception during treatment and for 12 weeks after treatment ends [see Warnings and Precautions (5.1)].

5. If a patient becomes pregnant while using ZOLADEX for endometriosis or endometrial thinning, ZOLADEX treatment should be discontinued. The patient should be advised of the possible risks to the pregnancy and fetus, including an increased risk of pregnancy loss [see Contraindications (4.2) and Use in Specific Populations (8.1)].

6. Those adverse events occurring most frequently in clinical studies with ZOLADEX are associated with hypoestrogenism: of these, the most frequently reported are hot flashes (flushes), headaches, vaginal dryness, emotional lability, change in libido, depression, swelling and change in breast size. Clinical studies in endometriosis suggest the addition of Hormone Replacement Therapy (estrogens and/or progestins) to ZOLADEX may decrease the occurrence of vasomotor symptoms and vaginal dryness associated with hypoestrogenism without compromising the efficacy of ZOLADEX in relieving pelvic symptoms. The optimal drugs, dose and duration of treatment has not been established [see Dosage and Administration (2.3) and Adverse Reactions (6.5) and (6.7)].

7. The use of GnRH agonists in women may cause a reduction in bone mineral density. In women, current available data suggest that recovery of bone loss occurs on cessation of therapy in the majority of patients.

In patients with a history of prior treatment that may have resulted in bone mineral density loss and/or in patients with major risk factors for decreased bone mineral density such as chronic alcohol abuse and/or tobacco abuse, significant family history of osteoporosis, or chronic use of drugs that can reduce bone density such as anticonvulsants or corticosteroids, ZOLADEX therapy may pose an additional risk. In these patients the risks and benefits must be weighed carefully before any therapy with ZOLADEX is started [see Adverse Reactions (6.10)].

8. Currently, there are no clinical data on the effects of retreatment or treatment of benign gynecological conditions with ZOLADEX for periods in excess of 6 months [see Dosage and Administration (2.3)].

9. As with other hormonal interventions that disrupt the pituitary-gonadal axis, some patients may have delayed return to menses. The rare patient, however, may experience persistent amenorrhea [see Drug Interactions (7.1) and Clinical Studies (14.3) and (14.4)].

10. Injection site injury has been reported following injection of ZOLADEX. Inform patients to contact their doctor immediately if they experience any of the following symptoms: abdominal pain, abdominal distension, dyspnea, dizziness, hypotension and/or any altered levels of consciousness [see Warnings and Precautions (5.9)].